

REMARKS

Claims 69, 72-75, and 78-129 are pending. Claims 69, 72-75, 78-82, and 88-129 are under examination.

Applicant has reviewed the Office Action mailed March 19, 2008, and respectfully traverses all grounds of rejection for the reasons that follow.

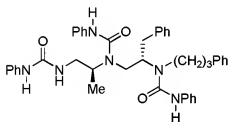
**Rejection under 35 U.S.C. §103**

Claims 69, 72-75, 78-82, and 88-129 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Nefzi et al. "An efficient two-step synthesis of mono-, di-, and triureas from resin-bound amides," Tetrahedron Letters, 2000, (41), pages 5441-5446.

Applicants wish to make two points of clarification based on statements made by the Examiner at the outset of this rejection.

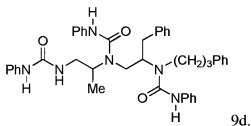
Firstly, the Examiner points to an issue of stereochemistry as discussed in the previous response to the Office Action of June 29, 2007. The Examiner alleges that Nefzi et al. discloses a compound having a CAS registry number of RN 295343-42-9.

To clarify, the stereochemistry explicitly shown in the CAS search conducted by the Examiner is as follows:



RN 295343-42-9

In contrast, the stereochemistry is not explicitly shown in the Nefzi reference. Rather Nefzi discloses a compound 9d as follows:



Nefzi appears to be silent regarding any adverse effects, due to the transformations in the synthetic scheme, on the stereochemical integrity of the chiral centers. Absent such comment, one skilled in the art would recognize that stereochemistry is frequently omitted in drawings in the peptide chemical literature for simplicity and clarity. The present application appears to use the same convention. What should be clear at this point, however, is that the common genus of claims 69 and 75 does not include a compound represented as 9d or a compound represented as RN 295343-42-9 because in those claims substituent  $R_1$  does not include methyl (sometimes shown as  $CH_3$  or Me).

As a second point of clarification, Applicants wish to point to an inadvertent error in stating the nature of the substituent at  $R_3$  in claims 69 and 75, which corresponds to substituent  $R_1$  in Nefzi et al. Applicants previously stated that Nefzi et al. disclose a phenylpropyl substituent off the nitrogen bearing the carbonyl and phenyl amino groups. This appears to be correct. However it was misstated, without deceptive intent, that none of the moieties defined by  $R_3$  of the Applicants' claims provide a phenylpropyl moiety. One of the defined substituents of  $R_3$  is a phenylethyl group. That group, taken together with the methylene group to which it is attached, would provide a phenylpropyl group.

In the present rejection under 35 U.S.C. §103(a) over Nefzi et al. the Examiner alleges Nefzi et al. renders obvious to one of ordinary skill in the art the creation of a TPI-927 analog with a phenylethyl at position  $R_3$ , or "other well known/structurally related variants/analogs/homologs (namely functional equivalents off the 3 R groups stemming from the required core structure..."

Applicant respectfully points out the following deficiencies with regard to the aforementioned rejection: The Examiner has not established a *prima facie* case of obviousness because 1) Nefzi et al. fail to teach all the claim elements of independent claims 69 and 75; and

2) there is no suggestion to alter the structures of the compounds as taught by Nefzi et al. to arrive at the compounds of the independent claims 69 or 75.

The examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3 1531, 1532, (Fed. Cir. 1993). Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. *Id.* at 1532. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 f.2d 1071, 1074 (Fed. Cir. 1988).

To support a *prima facie* finding of obviousness, it is required that the prior art references must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). There must also be some guidance either in the references themselves or in the general knowledge of skill in the art to motivate combining the references. Further, there must be a reasonable expectation of success in the combination suggested. These requirements have not been met with regard to the instant rejection.

Relevant to the case at hand regarding a *prima facie* case of obviousness for chemical compounds, the Examiner is respectfully asked to consider the following passage from *In re Deuel*:

“... a *prima facie* case of unpatentability requires that *the teachings of the prior art suggest the claimed compounds* to a person of ordinary skill in the art. \*1558 Normally a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties. Similarly, a known compound may suggest its analogs or isomers, either geometric isomers (*cis v. trans*) or position isomers (e.g., *ortho v. para*).

*In all of these cases, however, the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.* See *In re Jones*, 958 F.2d 347, 351, 21 USPQ2d 1941, 1944 (Fed.Cir.1992); *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed.Cir.1990) (*en banc*) (“*structural similarity between claimed and prior art subject matter, ... where the prior art gives reason or motivation to make the*

*claimed compositions, creates a prima facie case of obviousness"), cert. denied, 500 U.S. 904, 111 S.Ct. 1682, 114 L.Ed.2d 77 (1991); In re Grabiak, 769 F.2d 729, 731-32, 226 USPQ 870, 872 (Fed.Cir.1985) ("[I]n the case before us there must be adequate support in the prior art for the [prior art] ester/[claimed] thioester change in structure, in order to complete the PTO's prima facie case and shift the burden of going forward to the applicant."); In re Lalu, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed.Cir.1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.").* In re Deuel 34 USPQ2d 1210 (Fed. Cir. 1995), emphasis added.

Independent claim 69 has the claim elements of (1) a genus of chemical compounds (isolated agent) and (2) the agent derepresses an inhibitor of apoptosis protein- (IAP-) inhibited caspase. This second claim element is absent from the teachings of Nefzi et al. Thus, there is a lack of teaching of all the claim elements necessary in establishing a *prima facie* case of obviousness.

Further, Nefzi et al. lacks a suggestion to make the necessary changes in the chemical compounds taught therein to arrive at the compounds as claimed in independent claim 69. Nefzi et al. has at its centerpiece the teaching of a viable synthetic scheme to access substituted triurea structures, but there is no guidance or impetus to inspire the skilled artisan to make the changes in the structures presented therein to arrive at the claimed compounds. Nefzi et al. only teach how to make compounds of the structural class, not that the compounds have value as agents that derepress an inhibitor of apoptosis protein- (IAP-) inhibited caspase or what structural changes might be beneficial to impart such activity. In this regard, Applicants would like to respectfully point out that the Examiner has erred in characterizing Nefzi et al. as disclosing the products "intended use" as it relates to independent claim 69 and 75.

Independent claim 75 is patentable over Nefzi et al. for the same deficiencies in establishing a *prima facie* case of obviousness. Nefzi et al. fails to teach the claim limitations because claim 75 is directed to a complex comprising an IAP bound to an agent (the same genus as claim 69). Nefzi et al. is silent on any complex formation with triureas. Again there is no suggestion to make modifications to the chemical structures as disclosed in Nefzi et al., including generating any kind of complex with an IAP. For these reasons, the Examiner has failed to establish a *prima facie* case of obviousness.

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The remaining dependent claims depend either directly or indirectly from claims 69 or 75 and should therefore be patentable for at least the same reasons. Withdrawal of these rejections is respectfully requested.

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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